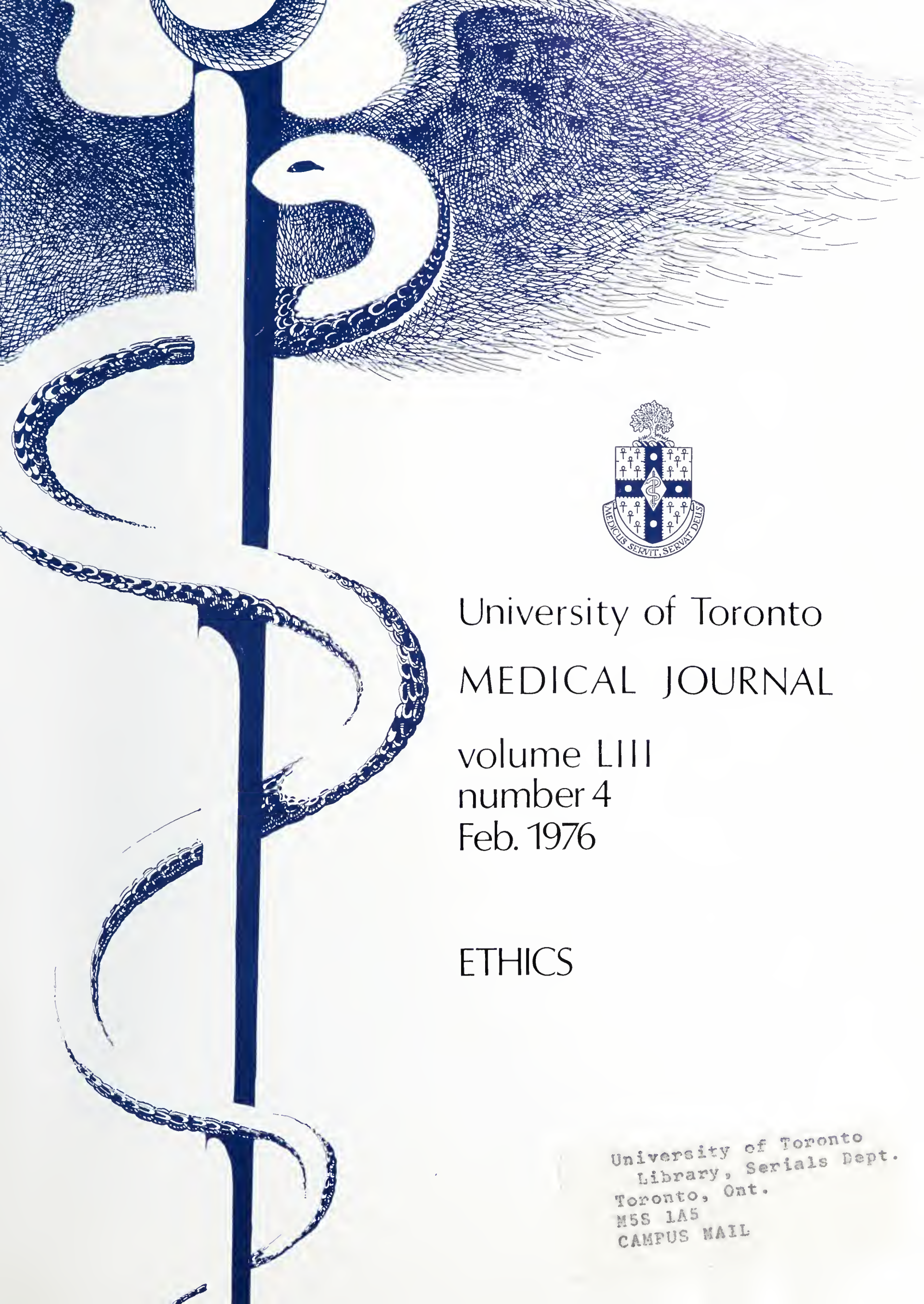

University of Toronto MEDICAL JOURNAL

volume LIII
number 4
Feb. 1976

ETHICS

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the UNIVERSITY of TORONTO MEDICAL JOURNAL

Established December 1923
An Undergraduate Publication

Volume LIII
Number 4
February, 1976

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Guest Editorial

DR. TOM PORTER was born at Dundalk, Ontario, in 1929, and attended school in Dundalk, Leaside and Toronto. He graduated from the University of Toronto Medical School in 1952, and after serving internships at Orangeville and Toronto East General Hospitals, commenced practice with his brother in the town of Unionville.

In 1954 he left practice to become an administrative medical officer with Physicians' Services Incorporated. He left PSI at the end of 1963 to accept a position as an Assistant Secretary with the Ontario Medical Association. He served for several years on the Ethics Committee and in 1973 was appointed General Secretary of the Ontario Medical Association.

Dr. Porter lives in Willowdale with his wife and four daughters. He is closely associated with the work of the Northminster United Church, where, in addition to serving on the Board, he is Superintendent of the Sunday School.

Speaking recently to a group of journalism students at the Ryerson Institute, Pierre Berton said that he did not consider journalism to be a profession because it did not have a code of ethics.

Traditionally, the writing of, and adherence to an ethical code have been hallmarks of a profession. It therefore behooves any group claiming to be a profession to be sure that its ethical code is a useful guide, because the difference between a group which has no code and one which has a code that of is no help is academic.

Few things are timeless, but ethical principles should approach this characteristic. But do they? No one in your university would hesitate to advise a patient to have a lithotomy, but Hippocrates felt it necessary to include in his oath the statement that he would never "use the knife . . . on sufferers from stone."

No matter how necessary it is from time to time, nothing could be much more dreary for this editorial than a long recital of ethical principles and an analysis of their current application. Rather, I would like to think on one or two ethical problems which face physicians in our society and question whether or not we have ethical answers for them.

Well what about euthanasia? Surely not a new problem, but certainly one given a couple of new and ironic twists by our own advances in knowledge. For example, we have a patient following a car accident or major surgery perhaps, started on life-saving machines with the sole intent of maintaining his life until, with or without additional intervention, he recovers. But he just does not recover. He does not regain consciousness; without the machine he would die. What do we do? To what ethical principle do we turn? The age-old reverence of life, of course. But what definition will we give "life"? Or to ask the question a different way, will we modify that principle to a "reverence for *meaningful* life"? And if we decide to end what appears to us to be meaningless life, is it acceptable to keep this life going for a few days more to see if we can find a recipient for his kidneys or his eyes? Indeed what is the difference between this patient, this life, and the one we saw and, knowing that he could never recover, attached the machines to keep "life" going in his kidneys until we could arrange for a recipient? Surely with both patients our motives have been the noblest. Yet with the latter one we do not hesitate to take the organs and disconnect the machines. With the former we wait and wonder and some of our colleagues go through court cases because the patient's family cannot stand the anguish any longer.

Questions! Rhetorical questions! A classical editorial cop out! Well, not quite. If you care to read back through the examples above, back through the questions, you will find the intrusion of members of society other than the doctor and the patient. And they cannot be ignored. Both doctor and patient live as members of other groups – families, medical staffs, other patients, churches, and social groups within which we act and which interact with each other. We cannot ignore the patient on repeated dialysis while we nurture the patient who will never live another meaningful day, but whose kidneys are working.

The point is that the study of ethics and the development of an ethical code must be a dynamic process. And it must take cognizance of the practical ethical problems and social attitudes faced by the people who will use it. Finally, our code must consider the doctor, the patient and their position together in society as a whole.

Euthanasia: A Survey of Medical Opinions

Timothy P. Barbetta, 7T8
Maureen Clement, 7T8
Leslie G. MacMillan, 7T8
Bruce R. Marshall, 7T8
Alfred O. Wong, 7T8

INTRODUCTION

"Vex not his ghost: O let him pass! He hates him
That would upon the wrack of this tough world
Stretch him out longer."

William Shakespeare
King Henry IV

Man has a tradition of respect for human life. It has not always been honoured, but, especially in recent years, man has developed an overall appreciation of the concept that human life is not to be treated callously.[1]

Today, however, we are faced more and more frequently with the question of euthanasia, "the bringing about of gentle and easy death, especially in cases of incurable and painful disease".[2] At first glance (and for many people, at all succeeding glances) the very idea seems to be in direct conflict with respect for life, since to affirm the morality of euthanasia is to embrace an act of killing as a good thing, not as a necessary evil as in war or self defence.

Heightened concern for euthanasia today is paradoxically a result of great strides in medical science during the past century. Most of history's great killers – the infectious diseases that attacked the young and prevented them from growing old – have been eradicated;[3] consequently, life expectancy has increased two-and-one-half-fold since antiquity, and two thirds of us can aspire to reach seventy years.[3] The result has been that today's big killers are the degenerative diseases such as heart disease, malignancy, and renal failure. The question has been raised whether the attitudes and techniques used in combatting untimely death (ie, in the young) are an appropriate frame of reference for viewing death in the "December" of life.[3] Compounding the issue is the fact that therapy directed against one event may only serve to expose another. And of course we have a whole armamentarium of machines which allow us to keep alive patients who in the past would have presented no ethical problem.

Euthanasia occupies a sort of legal limbo. It is quite clearly illegal, according to the Criminal Code of Canada, which considers everyone who intentionally causes the death of a human being to be guilty of murder.[4] In addition, the law provides that "everyone who undertakes to do an act is under a legal duty to do it if an omission to do the act is or may be dangerous to life".[4] In law, the definition of commission as opposed to omission is also important. An act of commission resulting in death is just as illegal for a doctor as for anyone else but the legal status of an act of omission derives from the doctor-patient relationship, rather than from the legal principle of sanctity of life.[5] This gives the physician considerable leeway in deciding what treatments offer any real hope of cure.

Against this review of statute law should be counterposed some case law. No physician has ever been convicted of murder or manslaughter after killing a patient in the name of mercy.[6] Numerous cases of even lay persons being treated considerably less strictly than the law provides are on record.[7] In short, while the law does quite expressly forbid active euthanasia, juries are less likely to convict or punish. Regarding traditional passive forms, the law seems content to demand that doctors practise their art with due skill and concern and to trust in the workings of the doctor-patient relationship beyond that.

The moral dilemma that is euthanasia revolves around the precise nature of human life and its position in the universe. At once we are led to other problems. To what limits must we go in our attempts to preserve life? What value judgments may we make concerning the quality of life? What responsibilities does the doctor have to his patient? to the patient's family? to society? Does a person even have the right to ask that his life be ended? Writers for various ethical theories (situation ethics, utilitarianism, and Roman Catholic natural law being the most active) have been arguing the problem for several centuries, but there is hardly space to do them justice. The interested reader is referred to the bibliography for elaboration.[8-12]

We wanted to get a feeling for current attitudes in in the medical profession toward euthanasia; we did not attempt a rigorous statistically significant survey. We interviewed thirteen doctors and four hospital nurses, asking the questions given in the body of this report. The group of doctors consisted of one obstetrician/gynaecologist, one paediatrician, one neurosurgeon, two unspecified staff physicians, one doctor involved in a clinical trial in cancer research, four family practitioners, two residents and one intern. All were male except for one of the GPs. Most were between forty and fifty years old but one was semi-retired and over sixty-five. All the nurses were female. Here, then, is what they had to say:

RESULTS

Doctors

Question 1: Do you think a patient has the right to ask for termination of his life?

Question 2: What do you feel is the responsibility of the doctor when a patient asks for euthanasia?

Responses to these questions are conveniently presented together.

Unanimously, the answer to the first was that the patient did indeed have the right to request termination. No stigma was attached, nor were any religious references made by any of the physicians interviewed. At the same time, however, it was also unanimously felt that such a request was not to be carried out except in very infrequent cases.

The most frequent explanation encountered for this position was that such requests are most often symptomatic of a transient state of profound depression in the patient, a state which some felt would probably pass and which others felt could and should be treated, either by the use of drugs or by psychotherapy. One physician told us that his ploy seems to work extremely well. It consists of a flat refusal, backed up if necessary by his advising the patient to secure another physician if still insistent upon his request. This was the most dramatic approach suggested.

Almost all of the doctors interviewed expressed the opinion that a doctor's first responsibility towards a terminal patient is to ensure that he is kept as comfortable as possible. Of primary importance is the relief of pain. Here, several recommended the use of drugs such as morphine, stating that even though its continued use might lead eventually to doses large enough to accelerate death, such use is both ethically and legally acceptable. It is obviously a very convenient measure because it generally relieves the patient's depression as well as his pain and, in this manner, is an acceptable means of shortening the terminal period. It was generally agreed, however, that an overdose designed to accelerate death was not acceptable. Interestingly, the one exception to this last point of view was voiced by the only physician having an extensive background of country and small town practice. He had previously stated that it was generally preferable for both patient and relatives that a terminal patient remain at home rather than in hospital, because of the likelihood of more attentive and loving care. He went on later to say that in a home situation it is much easier to administer an overdose of drug than at a hospital, where detailed records are kept and can be scrutinized by others. It was quite apparent that under some circumstances he has had reason to feel that an active step toward euthanasia was indicated.

Question 3: What are the bases for continuing treatment for terminal patients?

There were several aspects discussed. As mentioned before the consensus was that the primary goal of such treatment was to provide comfort and minimize pain in the patient.

The most fundamental aspect in continuing treatment must be the consideration of the benefits that might be derived from such treatment both in the patient and the family. Referring to this aspect, one group of doctors mentioned that "length of life" and more importantly, "quality of remaining life" be key guidelines regarding treatment. That is, the patient should be treated as proficiently as possible so long as he has the physical, mental and personal integrity for life.

An interesting comment was made by one physician concerning treatment. According to him the best form of treatment, at least psychologically, was merely the continuation of treatment. Apparently it is very important for the morale of the terminal patient that the doctor does not give up on him. Thus continued treatment will, if nothing else, improve the quality of remaining life.

There are several other factors which complicate the decision to continue or discontinue treatment. For example, shortage of equipment, long term supportive therapy and economic factors often force the doctor into considering other variables in his treatment of the terminal patient. Such factors as age, prognosis and overall personal situation might well be considered in these cases.

The concept "quality of life" seems very expansive and ill-defined. Thus, with most of the doctors interviewed, continuation of treatment was very dependent on the particular patient and circumstances involved. From an interview with a neurosurgeon, however, it seemed that this specialty is able to deal with the question of continuation of treatment in a more clear-cut manner than perhaps any other specialty. The reasons for this are fairly obvious. For one thing, classical brain death has been specifically defined by various medical associations, and discontinuation of supportive therapy in such cases is legally recognized. Secondly, there are a number of severe congenital neurological abnormalities which many hospitals have decided not to actively treat. Once more, an act of omission is seen as being more acceptable than an act of commission.

In summary then, the basis for continuing treatment in terminal patients is to actively treat the patient until his disease has removed all quality from his life, appreciating that "quality" is a subjective judgment.

Question 4: Under what conditions do you feel a doctor can justifiably decide to terminate the life of a patient?

All the doctors except one responded in a similar way. The question itself seems to have connotations toward active acts of euthanasia. One doctor (country practice) said that there possibly were a few instances where an active step might be justifiable. However, all the other doctors interviewed agreed that an active step was never justified in the medical care of a terminal patient. Instead, various passive acts may be used according to the condition of the patient. Many of the doctors believed that the decision to use passive euthanasia should not be left to one doctor but should instead be made by a panel of doctors.

Question 5: To what degree should a doctor take into consideration the wishes of the family?

Answers to this question ranged from an extreme "Not at all" to an opposite "A great deal".

The unanimous concern was again for the comfort and well-being of the patient. All agreed that the patient's wishes come first – so long as they are expressed, and are for continuation of life. The majority agreed that in cases of comatose terminal patients or of newborn babies suffering from such things as meningomyelocele, the wishes of the relatives become a major concern.

In general, there appears to be two markedly different family attitudes. In one, the family wishes the patient to be made as comfortable as possible but does not wish the use of extraordinary or heroic forms of treatment. In the other, the doctor is told not to let the patient die, regardless of the extent of treatment necessary. Thus it is only very rarely that one encounters a relative who requests a positive act of commission. The frequency of relatives requesting termination of treatment is somewhat greater, though still low.

As might be expected, there was obvious correlation between the statements that each physician made regarding how he would respond to such requests and his attitude towards euthanasia in general, and acts of commission *vs* those of omission specifically. Those who were prepared to condone acts of omission under the right circumstances would consider such a request from relatives. Here, it is important to mention that several doctors stated that they would have serious reservations associated with the potential guilt feelings that might be felt by the relatives if their request was overtly carried out.

In discussing such guilt among relatives, one doctor cited a case where he had been asked by the father of a drowning victim showing a flat EEG to shut off the respirator. He refused. After the parents had left, he complied with the request, telling the parents that other indications had arisen confirming death. The parents were thus relieved of any cause for future guilt over the termination of treatment. Reference to this form of approach was made by other physicians as well.

One answer to this question was interesting for its singularity. Reference was made to "treatment designed for the benefit of the family as well as the patient". This doctor considered that in many instances where close relatives request that a life be terminated, it is an indication that they are themselves suffering a degree of distress that warrants treatment.

Question 6: Do you think the doctor has an obligation to present to his patient all *the available forms of treatment particularly when the prognosis for some of them is uncertain?*

It was generally felt that the doctor had an obligation to present those forms of therapy, including surgery, which had a reasonable expectation of improving the quality of remaining life.

Most doctors felt it was necessary to consider the patient's personality and mental state when recommending forms of treatment. A person in the "bargaining stage" of dying may be willing to undergo an operation that has a very poor outcome and involves a lot of pain but may prolong his life for a short time. The doctor who has seen the situation before will most likely not even present this alternative to the patient.

Question 7: Should the terminal patient be informed of the final diagnosis?

Two different approaches were encountered. The first is that patients are not informed unless they specifically ask for details. In many cases, once the patient becomes suspicious, he does not wish to be told. However, the closest relatives are usually told about the final diagnosis and progress of the case. In the second approach, the physician tells the patient and his family about the definite diagnosis as soon as possible because future communication and treatment are not possible if doctor and patient are hiding information from each other. At the same time, this approach eliminates the possibility that the patient finds out about the diagnosis from other sources, which may undermine the patient's confidence in his doctor. Moreover, the patient has more time to put his affairs in order.

Question 8: Do you think the terminal patient should be allowed to join a therapeutic research program? (Informed consent)

Most doctors think that the patient should be allowed to join so that he has a chance to receive the new treatment and to benefit from it. In fact, for most therapeutic research programs the effectiveness of experimental treatment is at least of the order of magnitude of that in accepted protocols. However, patients should be clearly informed about the inherent risk and complications associated with most experimental procedures.

Question 9: What do you think about the concept of death as treatment instead of something you must always actively resist?

This question was probably worded too strongly for use in an interview – we received responses such as "Totally unacceptable", "Too final", and even "Sounds like headline stuff to me". Most of the physicians interviewed dismissed the question.

NURSES

We felt that it was important to include the viewpoint of nurses, particularly since, as a group, they were internally consistent and since their attitudes differed significantly from those of the doctors.

Question 1: Under what conditions do you feel euthanasia is justified?

Most felt that the proper time for euthanasia, if there was such a time at all, was during intensive care in cases where the prognosis was hopeless. That euthanasia could be performed in any sort of convalescent atmosphere was rejected.

Question 2: What do you see as the doctor's responsibility to prolong or terminate life?

As long as the patient can be kept free from pain, then treatment should be continued.

Question 3: What do you feel you should do if your ideas conflict with those of the doctor?

For the most part, this question was not really considered relevant. There is very little a nurse can do other than transfer to another department.

Question 4: How do you help a patient to feel that he is dying in a dignified manner?

The most important aspects are to take time to listen to a patient when he is willing to talk of his death, and to avoid making the patient feel that he must maintain a "chipper" facade.

The focussing on short-term goals was stressed. This might be something as simple as the patient's being able to hold a spoon with less tremor than the day before.

Finally, all the nurses agreed that it was important to touch the patients to reassure them that one is in no way repulsed by their illness.

In general, the nurses appeared more strongly opposed than doctors to terminating life, both actively and passively. One nurse recalled that when asked repeatedly by a patient to terminate her life, she became angry with the patient, telling her that she had no right to ask someone else to assume her responsibility for such an act.

CONCLUSION

It is worth considering some of the opinions regarding what constitutes euthanasia and the comparison between those acts generally considered unacceptable and those that can be condoned under certain circumstances. Philosophically, it can be argued that there is no real difference between an act of commission and one of omission. Both involve a positive decision to seek some end; in both the end sought is the death of the patient.

Nevertheless, it was apparent from the interviews that physicians view the latter much less severely than the former, even to the extent of considering acts of omission to be indicated in certain cases.

The difference between the two appears to be determined by whether or not the natural course of events is accelerated. Thus, ceasing administration of a drug, or failing to resuscitate after a cardiac arrest constitutes a decision not to interfere further with nature. They are acts of omission. Acts of commission, on the other hand, bring about death more rapidly than it would occur naturally, such as by the administration of drug overdoses. But, surely, medicine exists for the very purpose of altering the natural history of disease, so the argument becomes untenable.

The use of the respirator emphasizes the dilemma involved in starting a treatment when the prognosis is uncertain, especially since these procedures are often done in emergencies when the instinct is to act, to do *something*, rather than to weigh carefully the arguments for and against treatment. Failing to start a respirator would be an omission, but, once started, "pulling the plug" would probably be a commission.

We were surprised to find among doctors the degree of preoccupation with this issue that we did. We suspect it goes beyond legal considerations of guilt and of what goes on the death certificate, and is a manifestation of the physician's position on the "cutting edge" of the dilemma: he is called upon to act, rather than merely debate about how or whether one should act, and therefore he is much more conscious of what it means to lift one's own hand.

The last question asked of doctors concerning death as treatment is really the focus of the whole issue. A thoughtful consideration of it raises the issue of when do we stop trying to delay the inevitable and start thinking about what will be best for the patient. The whole *raison d'etre* of medicine is the conquest of disease, and expansion of the limits within which life can be maintained – in short, problem-solving in a clinical setting. Doctors are just not trained to view death as other than a tactical defeat. The pressures of our training require us to react with avoidance of emotional concerns (such as death) that threaten to interfere with our acquisition of knowledge; consequently, when we cannot avoid them we are left grasping at straws for answers. We lack the ability to deal with death comfortably, as a natural occurrence. We should indeed consider the question of Dr. Russel Elkington, writing in *Annals of Internal Medicine:* "When Adam and Eve ate of the fruit of the Tree of Knowledge, they lost their immortality. Do we really want it back?"[5]

It is interesting to speculate on the differing opinions of Doctors and Nurses. Two factors were felt to play a role. Nurses generally are limited by contact in the acute care situation and are therefore unaware of long term implications of maintaining some patients (eg, the spina bifida baby with mental retardation who may be a factor in the break-up of a marriage). In addition, it was felt that some nurses develop an emotional bond with their patients which prevents a truly objective analysis of the individual case.

SUMMARY

This project was undertaken to examine physicians' and nurses' attitudes toward euthanasia. Although the sample was small, the results were revealing, informative, and indicative of the soul-searching that doctors must undergo when faced with caring for the terminal patient and anticipating his death, a task that they are neither professionally nor psychologically equipped to execute. We would recommend that a multi-disciplinary course in medical ethics be incorporated into the curriculum in Period II or III as soon as possible. The course could include clinicians, ethical philosophers and religious leaders, and could have as its goal the education of physicians in how to think in ethical terms, so that when we have to face euthanasia and other ethical issues, we can make our decisions rationally, rather than by rationalization.

ACKNOWLEDGEMENT

The authors extend their appreciation to Dr. Merrijoy Kelner, Dept. of Behavioural Science, for her assistance and guidance in the preparation of this paper.

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(Cont. on page 83)

The Effects and Mechanism of Vasoactive Drugs on Adenosine Metabolism

Kirby Hsu, 7T9

INTRODUCTION

The requirements for oxygen in the myocardium are met by adjustments of coronary blood flow.[1, 2] An increase in coronary flow has been observed to correlate with increased adenosine in the blood.[3, 4] According to the adenosine hypothesis,[5] in response to a decrease in oxygen tension, the myocardium releases adenosine, which acts as a vasodilator, thus restoring oxygen tension by increasing coronary flow. There is, in addition, evidence to indicate that adenosine may play a role in cerebral blood flow in concordance with the proposed adenosine hypothesis.[6] Furthermore, coronary sinus blood in patients with a record of angina has been measured to be 40 nmoles per 100 mls of blood.[7] This gives a physiological adenosine concentration which can be worked with in experimental studies. The exact mechanism of vasodilating effect by adenosine is not clear, but it has been hypothesized that it is mainly dependent on its 6-amino group, and unhindered 2′ & 3′ hydroxyls[8] (See Fig 1).

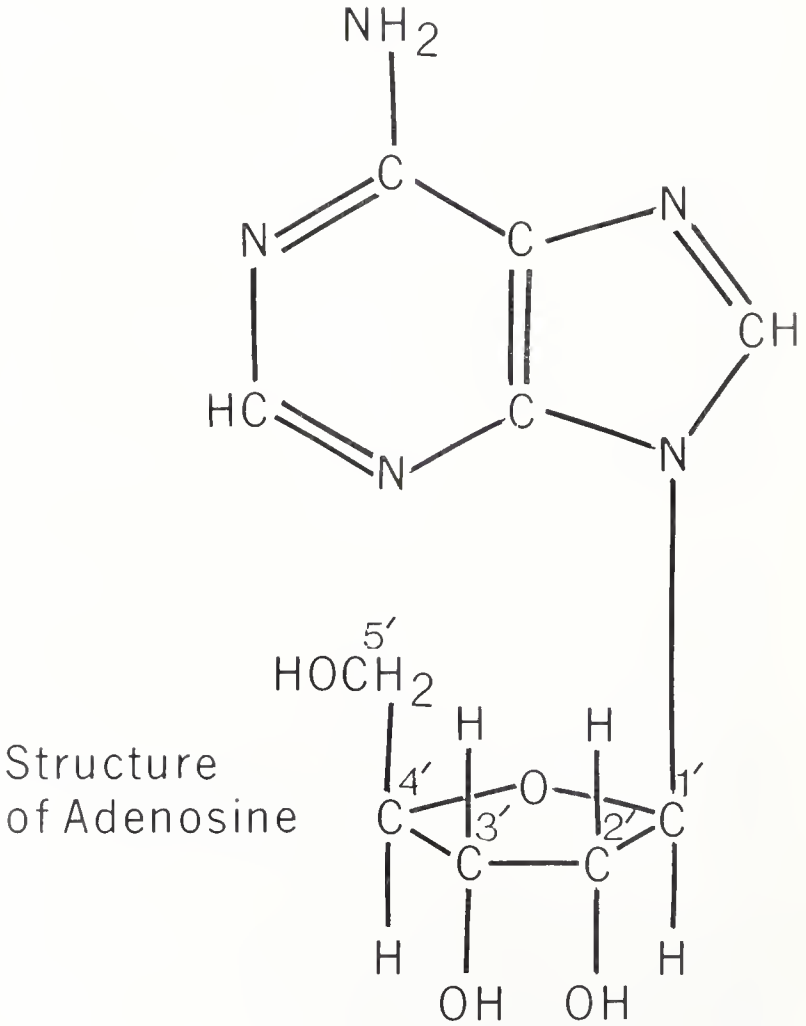

FIGURE 1. Structure of Adenosine

THE EFFECTS OF VASOACTIVE DRUGS ON ADENOSINE UPTAKE

Adenosine can be used as a vasodilator.[9, 10] It was found that Dipyridamole augments the vasodilating effect of adenosine.[11] When the phenomenon was studied in more detail, the observation was made that the enhancement of vasodilating effect by Dipyridamole was a result of inhibition of adenosine uptake by erythrocytes.[12] This inhibition of adenosine uptake is called the "adenosine-sparing" effect. In more recent years, new vasodilating drugs have been developed. They are Lidoflazine[13] and Hexobendine.[14] With these new discoveries, the question arises as to whether these drugs can induce the same adenosine-sparing effect as Dipyridamole. Indeed in studies that followed, it was observed that these drugs could inhibit adenosine uptake.[15, 16] In fact, adenosine-sparing effects of Dipyridamole and Lidoflazine have been demonstrated in lungs, erythrocytes, myocardium and other body tissues.[17] Moreover, it has been observed that at 0.1 mM Dipyridamole, uptake of 0.5μM to 5μM adenosine by erythrocytes was completely inhibited.[18] The results of these studies demonstrate the adenosine-sparing effect induced by these vasoactive drugs. The experiment done by the author in the summer of 1975 was an attempt to elucidate the mechanism of action of these drugs on adenosine metabolism. This is of clinical significance since it would lead to better control and management of a variety of cardiovascular diseases.

SUMMER PROJECT

Objectives:

The aim of the project was to induce the effects of Dipyridamole, Lidoflazine and Hexobendine on adenosine metabolism at adenosine concentrations of 20μM and 5μM, and to further investigate their effects at physiological adenosine concentrations (ie, 0.5μM). The effects of the above vasoactive drugs on adenosine kinase, adenosine deaminase and inosine phosphorylase were also investigated using human hemolysate (see Fig 3). Hemolysate is a preparation resulting from the lysis of erythrocytes.

Fresh erythrocytes were used to investigate adenosine metabolism because of simplicity and easy availability. They also serve as a good model, because they present both a transport barrier and a metabolic pathway for adenosine which are similar to cardiac muscle.[18] The metabolic pathway for adenosine in erythrocytes is shown in Fig 2.

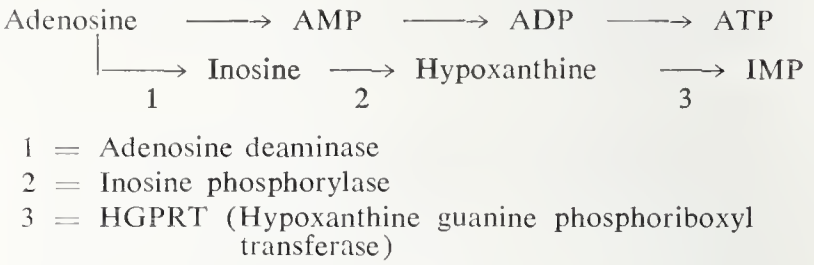

FIGURE 2. Adenosine metabolic pathway in erythrocytes.

Procedure:

1) For adenosine concentrations of 20μM and 5μM:– Fresh human erythrocytes were washed and centrifuged twice with normal saline at 4°C. An incubation medium

of a total volume of 100μl was made up of the following: RBC 15μl, normal saline 5μl, Tris-glucose 10μl pH 7.4, PO_4-Mg 20μl, (8-^{14}C)-adenosine 25μl, vasoactive drug 25μl. Drug concentrations were 100μM, 10μM, 1μM and 0.3μM for Dipyridamole and Hexobendine; 100μM, 10μM, 3.3μM and 1μM for Lidoflazine. Three different adenosine concentrations were used as stated above. The medium was incubated for 5 minutes at 37°C. The reaction was terminated by adding 25μl of 40% perchloric acid (PCA), and neutralized with 25μl of KOH after mixing thoroughly. The mixture was then centrifuged for 5 mins. at 2600 rpm. Each incubation was performed in duplicate. In one control medium 25μl of normal saline was substituted for 25μl of drug. In another control, perchloric acid and KOH were added to the medium before the addition of (8-^{14}C)-adenosine, thus ensuring no reaction. This was used as the blank.

From the supernatant of the centrifuged reaction mixture radioactive AMP, ADP, ATP, inosine, hypoxanthine, inosine monophosphate (IMP) and adenosine were separated and quantified as follows:

i) 25μl of each mixture was spotted onto a 3mm Whatman chromatography paper with 25μl of "cold" carrier. The paper was put into Borate buffer (pH 8.9) for high voltage electrophoresis (HVE). It was run for half an hour at 4,000 volts. Separation of inosine from adenosine and hypoxanthine was obtained.

ii) 25μl of each mixture with 25μl of "cold" carrier were spotted onto a 3mm Whatman chromatography paper and put into Citrate buffer (pH 3.5). The paper was run for one hour at 4,000 volts for HVE. Separation of adenosine from hypoxanthine and inosine was obtained.

iii) Lastly, 5μl of each mixture with 5μl of "cold" carrier were spotted onto PEI cellulose thin layer sheets. Thin layer chromatography was performed using 0.5M formate buffer (pH 3.4), then 2M formate and finally 4M formate to effect a separation of ATP, ADP, AMP and IMP.

The resultant spots on different papers were visualized under ultraviolet light and marked. These spots could then be cut and quantified in a scintillation counter after immersion in 10 mls of toluene phosphorus solution.

2) For adenosine concentration of 0.5μM, due to the low concentration on adenosine, U-^{14}C adenosine (uniformly labelled, ie, every carbon atom) was used in place of (8-^{14}C)-adenosine. The 100μl incubation medium was made up of the following: RBC 1μl, Tris-glucose (pH 7.4) 10μl, PO_4-Mg 20μl, normal saline 19μl, drug 25μl, U-^{14}C adenosine 25μl. These incubations were again performed in duplicate. In one control, normal saline was substituted for the drugs, and in another, PCA and KOH were added before U-^{14}C. This time extra precaution was taken to ensure that the radioactivity measured was not from metabolites other than the ones shown in Fig 2. This was done by adding 20μl of charcoal to a third control medium, which was then centrifuged and the supernatant was used for separation. Any counts that arose from this medium were due to impurities and had to be subtracted from all other counts. All other incubations, separation procedures and drug concentrations were the same as described in section 1 above.

The effects of vasoactive drugs on adenosine kinase, adenosine deaminase, and inosine phosphorylase were investigated using the same principles as above, except that hemolysate was used. This eliminated the transport barrier present in fresh erythrocytes (see Fig 3 for principal reactions).

Adenosine deaminase: Adenosine* $\longrightarrow$ Inosine*
$\swarrow$
NH_3†

Adenosine kinase: Adenosine* + ATP $\longrightarrow$ AMP* + ADP

Inosine phosphorylase: Inosine* $\longrightarrow$ Hypoxanthine*
$\nearrow$
Pi‡

* Radioactively labelled
† Ammonia given our during reaction
‡ Inorganic phosphate required for reaction

FIGURE 3. Main reactions used in the study of the effects on enzymes by vasoactive drugs.

Results:

Counts for hypoxanthine alone were calculated by subtraction of hypoxathine and inosine obtained by Citrate HVE from inosine obtained by Borate HVE. All other metabolites were counted separately. The results (Tables 1-4) are expressed as per cent of control. The total counts for AMP formation was determined from the sum of the counts of AMP, ADP and ATP; and the total counts for inosine (HR) formation was determined from the sum of the counts of HR, hypoxanthine and IMP.

An adenosine-sparing effect was observed. It was more marked at 20μM and 5μM concentrations (387% and 157% of control respectively) than 0.5μM (135% of control) (See Table 4).

With 20μM adenosine, AMP/inosine ratio varied from 1 to 3.5 for Dipyridamole, 0 to 5.4 for Lidoflazine and 0.13 to 2.13 for Hexobendine. This shows that adenosine phosphorylation (formation of AMP, ADP, ATP) predominates over adenosine deamination (formation of inosine, hypoxanthine and LMP). Similar effects were also observed at 5μM adenosine (See Table 1).

With 20μM and 5μM of adenosine, Dipyridamole, Lidoflazine and Hexobendine inhibited both adenosine phosphorylation and deamination at high drug concentrations (ie, 100μM and 10μM). An enhancement of AMP and nucleotides formation over control was observed at lower concentrations of Lidoflazine (ie, 3.3μM and 1μM). Similar enhancement effect was observed with Dipyridamole at 0.3μM, but not at any of the Hexobendine concentrations used (See Table 1).

With 0.5μM adenosine, AMP/inosine ratios were

		DRUG CONCENTRATION														
		100 μM			10 μM			3.3 μM			1 μM			0.3 μM		
Drug	AR[1]	AMP	HR*	AMP/HR	AMP	HR	AMP/HR	AMP	HR	AMP/HR	AMP	HR	AMP/HR	AMP	HR	AMP/HR
D[2]	20	7**	2	3.50	5	5	1.00	–	–	–	76	22	3.45	108	81	1.33
	5	11	4	2.75	8	24	0.33	–	–	–	89	51	1.74	110	84	1.30
	0.5	0	117	0	1	220	0	–	–	–	39	143	0.27	58	163	0.35
L[3]	20	0	7	0	49	9	5.44	108	49	2.20	102	78	1.30	–	–	–
	5	0	12	0	39	24	1.65	115	73	1.57	117	72	1.62	–	–	–
	0.5	0	240	0	4	227	0.01	48	119	0.40	71	117	0.60	–	–	–
H[4]	20	2	15	0.13	8	17	0.47	–	–	–	44	19	2.31	85	79	1.07
	5	2	9	0.22	0	12	0	–	–	–	20	22	0.90	53	92	0.57
	0.5	2	84	0.02	2	188	0.01	–	–	–	2	231	0	42	171	0.24

1. AR= adenosine concentration in μM
2. D= Dipyridamole
3. L= Lidoflazine
4. H= Hexobendine
* HR= Inosine
** Expressed as per cent of control

TABLE 1. Effects of Dipyridamole, Lidoflazine and Hexobendine on AMP and inosine synthesis.

much less than 1 in most cases. For Dipyridamole the ratio was 0 to 0.35, for Lidoflazine 0 to 0.60, and for Hexobendine 0 to 0.24. This means that at this adenosine concentration deamination predominates over phosphorylation. In all cases except one, inosine formation was augmented over controls. These inosine formations were marked by 117 to 231% of the control values (See Table 1).

There was also a general correlation of decrease in AMP/inosine values with a decrease of adenosine concentrations. This means that as adenosine concentrations are lowered, inosine formation is stimulated more than AMP formation. The effects of Dipyridamole, Lidoflazine and Hexobendine on AMP and inosine formation are summarized in Table 1.

There was no significant effect of the tested vasoactive drugs on adenosine deaminase and inosine phosphorylase. These results are shown in Tables 2 and 3. The experiments on adenosine kinase cannot be deemed conclusive, but preliminary results indicated inhibition of the enzyme.

Discussion:

The adenosine-sparing effect observed is in agreement with other studies.[17, 19] There have been two main mechanisms hypothesized to explain the inhibition of adenosine uptake: 1) the inhibition of adenosine transport into the cell, thereby inhibiting any form of metabolism, and 2) the inhibition of adenosine metabolism itself, phosphorylation or deamination, hence raising adenosine concentration.

It has been shown that adenosine kinase and adenosine deaminase are associated with the membrane of erythrocytes.[20] It has been proposed by Schrier that in the triple layer model of membrane, adenosine kinase is oriented inward and adenosine deaminase is oriented outward.[21] In our experiments, with adenosine concentrations above 5μM and drug concentrations above 10μM, both kinase and deaminase were inhibited, and this can be explained by nearly total inhibition of transport. At lower drug concentration (3.3μM and below), there was an enhancement of AMP formation over the control. This can also be explained by the transport mechanism in that adenosine kinase has a lower Km (5μM) than adenosine deaminase (20μM). With the small amounts of adenosine which were able to get into the cell at low drug concentrations, almost all of the adenosine was converted to nucleotides by kinase. This is in agreement with the results of other workers.[22, 23, 24]

At a physiological adenosine concentration of 0.5μM, adenosine kinase was very much inhibited even at 0.3μM of drugs. This was marked by AMP formation of 0 to 38% of control. Adenosine deaminase on the other hand was greatly enhanced, which was marked by the inosine formation of 84 to 240% of control. These observations have not been reported by other workers, and they do not appear to be readily explained by the transport mechanism. Our preliminary results showing inhibition of adenosine kinase by vasoactive drugs at 0.5μM adenosine is eompatible with the above observation. This is reinforced by our finding that AMP/inosine ratio decreases with decreasing adenosine concentrations.

		% Control	
Drug	Concentration (μM)	Adenosine	Inosine
Dipyridamole	100	99	79
	10	100	103
	1	85	95
	0.3	90	82
Lidoflazine	100	88	93
	10	99	99
	3.3	85	103
	1	104	91
Hexobendine	100	122	84
	10	121	91
	1	116	131
	0.3	124	107

TABLE 2. Effect of Dipyridamole, Lidoflazine and Hexobendine on adenosine deaminase.

Since the exact mechanism of adenosine transport is not known, it is possible that intracellular adenosine concentration increases with decreasing extracellular concentrations. Since kinase has a lower Km, it also

has a much lower activity.[22] Therefore, the transport mechanism may explain our observations at 0.5μM adenosine. Nevertheless, this does not rule out the possibility of a metabolic inhibition which deserves further investigation.

Drug	Concentration (μM)	% Control	
		Inosine	Hypoxanthine
Dipyridamole	100	108	94
	10	113	98
	1	112	98
	0.3	103	88
Lidoflazine	100	105	87
	10	101	97
	3.3	106	90
	1	102	79
Hexobendine	100	105	95
	10	101	89
	1	95	101
	0.3	103	86

TABLE 3. Effect of Dipyridamole, Lidoflazine and Hexobendine on inosine phosphorylase.

Adenosine	*Per cent of control**
20μM	387
5μM	1578
0.5μM	135

* Average of 3 percentages from Dipyridamole, Lidoflazine, and Hexobendine.

TABLE 4. Effect of vasoactive drugs on adenosine uptake.

SUMMARY

1) Adenosine-sparing effect induced by Dipyridamole, Lidoflazine, and Hexobendine was observed at concentrations of 0.3μM to 100μM.

2) Adenosine deaminase and inosine phosphorylase were not inhibited by the three vascoactive drugs tested from 0.3μM to 100μM.

3) AMP/inosine ratio correlates proportionally with adenosine concentration.

4) Adenosine uptake inhibition at 20 and 5μM concentrations can be explained by the transport mechanism.

5) Adenosine uptake inhibition at 0.5μM concentration is not fully understood. It may implicate an inhibition of adenosine kinase at this physiological range.

ACKNOWLEDGEMENTS

The author wishes to express special thanks to Dr. Irving Fox and the staff of the Rheumatic Disease Unit, Wellesley Hospital, University of Toronto for their assistance and guidance in carrying out this summer project.

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The Medical Importance of Fleas

James L. Kirkland, 7T7

Fleas have bothered man from time immemorial. Priests of ancient Egypt shaved their heads to avoid infestation, mummified fleas were found in the clothing of Henry VII, and Marco Polo told of Indian nobles who had their beds raised by pulleys attached to the ceiling to avoid the pests.[1] It is written that "The natives of Aitutaki, observing the fleas were constantly restless and inquisitive, and at times even irritating, drew the reasonable conclusion that they were the souls of deceased White men".[2]

Fleas are small (1 to 4 mm), secondarily wingless, laterally compressed ectoparasites of vertebrates. Their piercing-sucking mouthparts enable adults to obtain their sole food, blood.[3] Of the 1900 known species and subspecies of fleas about 1800 of these attack mammals and many attack man (Tables 1 and 2). Some varieties prefer to infest one type of mammal but many will bite any available mammal. The human flea *Pulex irritans* has been found on echidnas (small ant-eating mammals), skunks, mallard ducks and short-eared owls.[4] Starved fleas have been known to suck fluid from caterpillars.[5]

TABLE 1

Fleas which have attacked man in North America[3, 7, 8]

Eastern North America	preferred host(s)
Pulex irritans	man, pig, dog
Ctenocephalides canis	dog
Ctenocephalides felis	cat
Xenopsylla cheopis	rat
Echidnophaga gallinacea	poultry
Hoplopsyllus affinis	rabbit
Cediopsylla simplex	rabbit
Orchopneas howardi	squirrel
Ceratopsyllus gallinae	bird
Oropsylla arctomys	rodents, fox, deer, owl
Hystrichopsylla sp	wild rodents
Tunga penetrans	

Western North America	preferred host(s)
Pulex irritans	man, pig, dog
Ctenocephalides canis	dog
Ctenocephalides felis	cat
Echidnophaga gallinacea	poultry
Nosopsyllus fasciatus	rat
Diamanus montanus	squirrel
Dasypsyllus gallinulae perpinnatus	rodents, birds
Ceratophyllus niger niger	chicken
Hoplopsyllus anomalus	ground squirrel
Ceratophyllus garei	birds
Monopsyllus ciliatus protinus	chipmunk
Monopsyllus vison	pine squirrel
Monopsyllus eumopli eumopli	chipmunk
Monopsyllus wagneri wagneri	deer mouse
Oropsylla artomys	marmots, skunks, coyotes
Hystrichopsylla sp	wild rodents

Fleas are attracted to their hosts by a wide assortment of stimuli. Cat fleas are drawn by warmth, rat fleas by rat odour, and great jird fleas by vibration.[6] Other types are attracted by light, noise, temperature gradients, pressure changes and air currents. Fleas are attracted to women more often than to men, and it has been proposed that this stems from the sensitivity of certain fleas to their hosts' estradiol levels.[6] Fair skinned people (especially those with red hair) and children have a greater chance of becoming infested.[7]

In its development the flea undergoes complete metamorphosis. Flea eggs are 5 mm long, shiny, white and cylindrical. From three to eighteen are laid at a time, an average of up to three eggs per day. The female only oviposits when it has had regular blood meals. The eggs are dropped to the ground and hatch as worm-like larvae after two to twelve days. They feed on organic debris on the ground, beneath carpets and in cracks in the floor. They also eat adult flea excrement which contains iron necessary for cuticle formation. The larval stage may last nine to two hundred days and larvae may live up to one month without food.[7] The larva spins a translucent, loose cocoon and pupates seven days to one year. Although the adult fleas in a house may be eradicated, there can remain a large reservoir of eggs, larvae and pupae.

Adult *Pulex irritans* may live as long as 513 days and may survive 125 days without food.[3] Female fleas live longer than males and are larger. Fleas are hardy: they may survive nine months at –1°C.[6]

Fleas have thick cuticles. The dog flea, for example, is difficult to kill by rolling it between the pulps of the fingers. It may be necessary to pinch it between the fingernails, kill it with nail clippers, or immobilize it in vaseline (carbolated vasoline is toxic to fleas[8]).

Adult fleas live in the folds of clothing, in their host's bed and stuffed furniture, and on floors and carpets.[9] They can be very difficult to spot and their jump is too rapid for the eye to follow. *Pulex irritans* has been known to jump 7.5 inches vertically and 13 inches horizontally.[10] Fleas land facing the direction from which they came, enabling them to catch the clothing or hair of their host with their hind legs and the bristles on their abdomen.

Infested patients may catch a flea and bring it to their physician. They may give a history of ownership or even mere contact with a dog or cat.[11] Infestation usually occurs in the summer or fall. Often only one member of a family may have a reaction. If it is drawn to the patient's attention he may notice that his bed is gritty because of the crusts of blood, eggs, larvae and feces in it.

Irritation is produced by the secretions of the flea's salivary gland. The host's response may range from no reaction to serious delayed reactions.[12] It has been suggested that the IgE response to insect bites was originally protective. Oozing dilutes harmful salivary protein antigens, pruritus leads to mechanical removal of offending antigens, and the reaginic response induces avoidance behaviour in the host.[13] The most common manifestations of flea infection are zigzag lines or clusters of hemorrhagic punctae surrounded by erythematous patches on the ankles, legs or waist. The

TABLE 2

Some fleas which may transmit plague to man[5]

flea	host	location
Hoplopsyllus anomalus	ground squirrel	Western U.S.
Hectopsylla suarezi	cavies, rats	Equador
Hectopsylla eskeyi	cavies, rats	Peru
Delosticlus talix	cavies	Argentina
Xenopsylla phyllomae	gerbils	South Africa
Chiastopsylla rossi	rat	South Africa
Dinopsyllus ellobius	rodents	South Africa, East Africa
Synopsyllus ellobius	rat	Madagascar
Citellophilus tesguorum	ground squirrel	South East Russia
Frontopsylla senura	ground squirrel	South East Russia
Neopsylla setosa	ground squirrel	South East Russia
Nosopsylla sp.	gerbils, lemmings, mice	South East Russia, Iran
Oropsylla silantiewi	marmot	Mongolia
Stivalius cognatus	rat	Java

bites usually appear at the tops of the shoes and then on other parts of the body, but rarely on the arms and almost never on the face. Soothing lotions and corticosteroids may be used to treat these wounds. Topical antihistamines should not be used because they may cause an allergic reaction.

Fleas may produce papular urticaria (lichen urticatus), especially in children, ten to fourteen days after exposure. It has been estimated that 65 to 100 per cent of papular urticaria is caused by insects, and in about 75 per cent of cases fleas are partly or wholly responsible.[14] Papular urticaria appears as wheals and/or firm papules grouped in clusters on the extensor and exposed surfaces. It rarely occurs on the trunk. New crops appear at intervals and are pruritic, and the inevitable excoriations may become secondary infected. The lesions take several days to resolve. Papular urticaria is uncommon in adults; the lesions do not occur in clusters but their distribution is similar. The lesions may be treated with talcum powder. Abnormal reactions to flea bites include the development of delayed necrotic lesions with later discolouration which may last months,[12] and the appearance of multiple vesicles.[15]

Natural immunity to the effects of the bites may occur after prolonged exposure. Several flea antigens have been prepared from human, dog and cat flea extract in phenolated isotonic saline. Although these antigens may produce desensitization, they have been found to produce serious hypersensitization.[15] The use of such preparations remains limited.

Infestation with fleas is very irritating for a sensitized individual. Even after the infestation has been resolved a delusory parasitosis may remain. The patient may present with specimens of clotted blood or crumbs of toast which he believes to be fleas. He may insist he can see and feel parasites on his skin.[16] There may be small scattered superficial excoriations with surrounding erythema on the extremities and trunk. None of the lesions will be beyond the reach of his fingernails. The excoriations and secondary infections should be treated, but investigation may reveal a serious psychosis. In all cases it is necessary to make a careful search for an infestation.

Tungiasis is a serious form of flea infestation encountered in tropical and subtropical North and South America, the West Indies, Africa and India.[3] *Tunga penetrans* (jigger, chigoe, sand flea) was originally confined to America, and it infested Columbus' men on Haiti in 1493.[17] The insect was introduced into Africa in 1872 but probably had existed there earlier, and was carried by members of the Indian army to India. This flea, which burrows into the skin and can cause gangrene, became very common in parts of Africa. Albert Schweitzer wrote that it was rare for Africans to have ten toes intact because of the jigger.[1]

The jigger is reddish brown, 1 mm in length, and has a large angular head. The female's spiracles are in the posterior part of the abdomen. The gravid female burrows into the host's skin until only its spiracles protrude. The female grows several millimetres before passing its eggs to the outside and dying. Nigua or jigger cocoons surrounded by fibrous sacs in the skin of patients have been described.[9] However, the eggs, larvae and pupae only rarely develop on the host, and usually develop as do most other fleas away from the host.

The gravid female usually burrows between the toes, into the soles or ankles, or under the toenails of its host. Occasionally the insects burrow into the anogenital or other regions.[9, 18] They induce the formation of pruritic nodules the size of a pea which may develop into painful, secondarily infected ulcers. The lesions produced by numerous jiggers may form a confluent, pus-charged plaque which may lead to secondary tetanus or gangrene and autoamputation.

The entrance hole produced by the flea should be enlarged under sterile conditions, and the flea may then be squeezed out. The remaining wound should be debrided and dressed. Secondary infections may be treated with systemic antibiotics and the patient should be immunized against tetanus if necessary. Tungiasis may be prevented in endemic areas by wearing shoes or using flea repellants. *Tunga penetrans* is not a known disease vector.

FLEAS AS VECTORS OF DISEASE

Certain fleas not only produce irritation of the skin, but are also vectors of serious disease. Fleas are the

major vectors of plague and endemic typhus, and are also vectors of the rat tapeworm, dwarf tapeworm and double-pored dog tapeworm. Fleas are also a vector of myxomatosis, an economically important rabbit disease,[3, 4] and may act as a vector of the Friend leukemia virus.[19] Contrary to past belief it is unlikely that fleas are an important vector of tularemia.[20]

A. Plague

Plague is primarily a disease of rodents and is endemic in rodent populations in India, East and Central Asia, South America, Western North America and Mexico.[3, 5, 21] It is spread from rodent to rodent by a number of flea species and periodically causes disastrous human pandemics. In the fourteenth century a quarter of the population of Europe succumbed to the disease. The last major pandemic began in China and had spread to North America by 1900. By 1904, 122 cases occurred in the western United States and several localized epidemics followed. Plague was epizootic in ground squirrels in Alberta in 1939 and it is possible that one case of human plague resulted.[7] From 1935 there have been one or two cases annually until the summer of 1965 when there were six cases in New Mexico.[22] Forty-one cases have been reported in North America between 1966 and 1974, many of whom were military personnel returning from South East Asia.[23] Although presently on the wane, plague may at any moment erupt again.[24] Pollitzer writes, "As history teaches, plague has often shown a decline even if left alone, but was apt to flare up again in due course".[25]

It was not until 1897 that Ogata showed that fleas were plague vectors.[5] Some of those which may transmit plague to man are listed in Table 2. This disease is most often spread among men by droplets.

Plague bacilli from an infected blood meal multiply among the spine-like epithelial processes of the flea's proventriculus (Figure 2). The bacilli and blood form a tarry clot which "blocks" the proventriculus, and the flea is unable to swallow. Blocked fleas are ravenous and try to feed often. When they bite, the blood ingested comes in contact with the infected plug and causes distension of the esophagus. The elastic recoil of the esophagus forces infected blood into the victim. Plague may rarely be spread by inhaling or rubbing into skin abrasions the infected flea feces.[26]

Many factors affect the extent of epidemics. The species of flea and the proportion of each which infest infected rats is important. Fleas which feed at short intervals (eg, *Xenopsylla cheopis*) are more likely to contact an infected host that those which feed at longer intervals (eg, *Nosopsyllus fasciatus*). *Xenopsylla cheopis* begins to search for new hosts after its plague-infected host has been dead fifteen seconds. Other fleas (eg, *Echidnophaga gallinacea*) may remain attached until their own demise. The proventricular blockage rate varies, and the blocking rate depends partly on the concentration of plague bacilli ingested.[27] The length of time infected fleas survive is important; some have lived 206 days.[5]

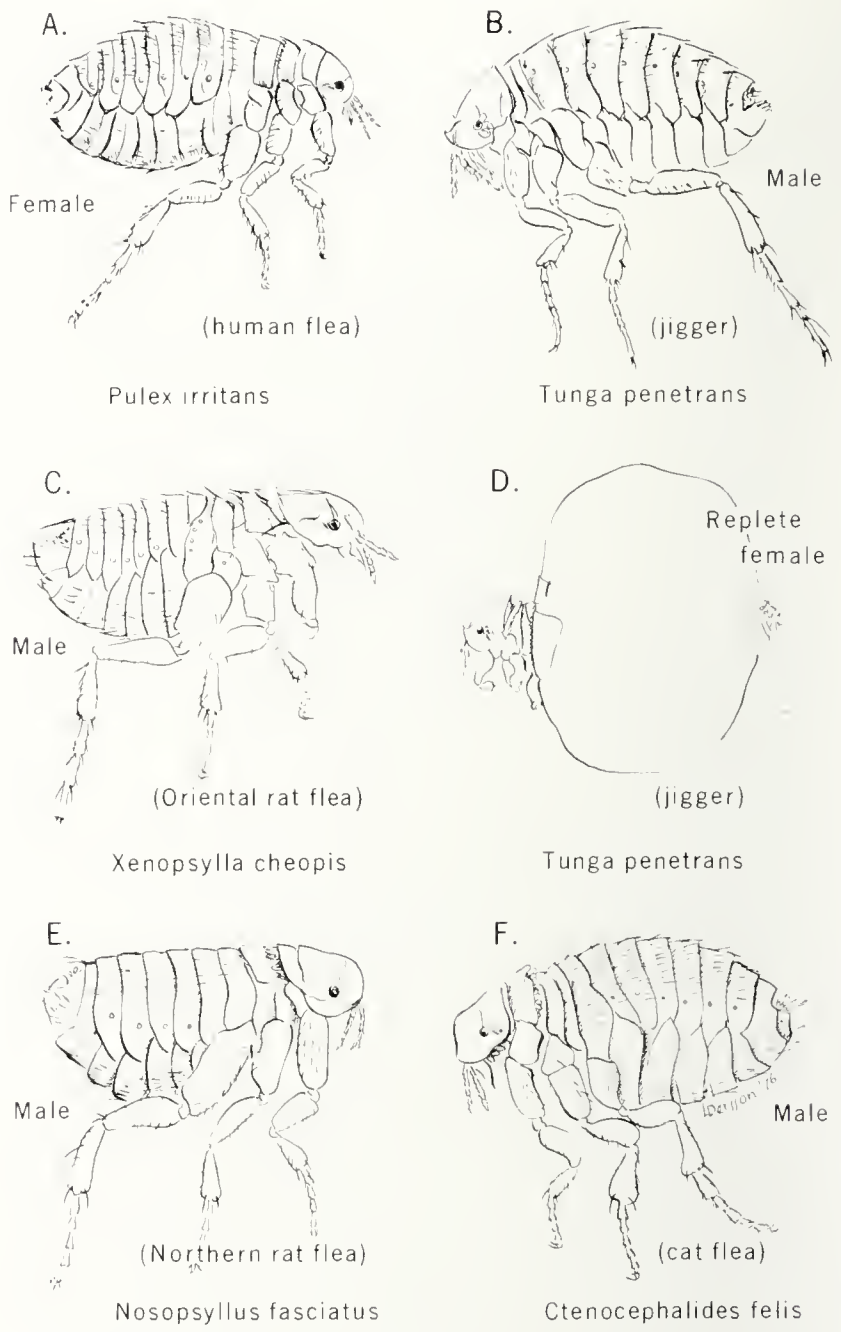

Figure 1
Common Fleas which are Human Disease Vectors
(After James and Harwood[3] and Hubbard[7])

Rattus rattus is usually the infected host of fleas which spread plague to man, but other animals are infested by fleas which can transmit the disease to humans (Table 2). Wild rodents are the most important reservoir, and may contact *Rattus rattus* or other domestic rodents at the fringes of cities. An exchange of fleas may occur and plague may become epizootic in the city rats.

The spread and severity of plague depends on the strain of *Yersinia pestis*, the plague bacillus. Some strains are likely to clump and produce ventricular blockage while others tend to pass through the flea's gastrointestinal tract and produce infected feces. Some strains are not virulent in humans. *Y. pestis* is a short, non-motile gram-negative rod producing several toxins which depress heart muscle mitochondrial activity, produce a change in vessel tonus, and induce a hemorrhagic tendency which causes black patches (hence the name "Black Death"). At the site of the bite a plague pustule appears in 5 per cent of cases.[5] The infection spreads along lymphatics to regional nodes to produce a hyper-

plastic, hemorrhagic inflammation, the bubo.[28] The infection may spread through efferent lymphatics to the systemic circulation.

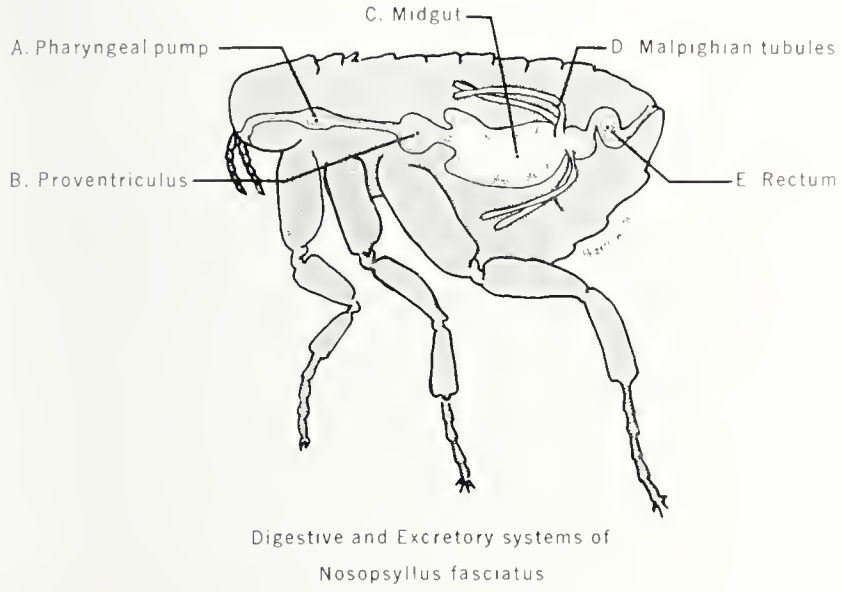

FIGURE 2
Digestive and Excretory Systems of *Nosopsyllus fasciatus*
(After James and Harwood[3] and Rothschild[6])

About three days following the infective bite, the patient has chills and fever. There is headache, prostration, tachycardia and vomiting, and there may be splenomegaly and pericardial, pleural and peritoneal effusions. Petechiae and ecchymoses may appear and visceral bleeding occurs. Sixty to 90 per cent of untreated cases are terminal, usually in the first week.[7] Recovery results in lasting immunity against reinfection.

Early treatment is necessary to prevent toxemic death. Streptomycin alone or in combination with tetracycline is the drug of choice. Buboes may be treated with hot wet compresses and may be surgically drained only after twenty-four hours of streptomycin. Cases should be isolated and reported to public health authorities. Sulfonamides, tetracyclines or streptomycin may be used as prophylaxis in exposed individuals. A vaccine which imparts temporary incomplete protection may be given to those likely to be exposed or to travellers to endemic areas.

B. Typhus

Endemic typhus, or murine typhus, is spread to man from rats by fleas. The disease was first recorded in North America in New York in 1898 and was found to be endemic in the southeastern United States.[29] Untreated, the disease has a 0.5 to 2 per cent case fatality rate.[29, 30] The main reservoirs are *Rattus rattus*, *Rattus norvegicus* and wild mice. The infection in these rodents is inapparent in the enzootic state and may be recovered from an animal a year after its exposure. Periodically the disease becomes epizootic, associated with high rodent mortality, as fleas search for alternate hosts.

The most important vectors from rats to humans are *Xenopsylla cheopis* and *Ctenocephalides felis*, the cat flea. The causative organism, *Rickettsia mooseri*, multiplies in the flea's intestinal cells and is excreted in the feces for as long as 651 days after exposure.[7] The feces are infective if they are rubbed into skin abrasions, are inhaled or contact the conjunctiva. It is unlikely that direct man to man transmission occurs, but the body louse *Pediculus humanus* may transmit the disease among men.

The disease is usually sporadic although it may approach epidemic proportions. Presently there are less than one hundred cases annually in the United States.[30] Endemic typhus occurs in harbour cities in the late summer and fall among food handlers, and many patients give a history of contact with fleas.

Rickettsia mooseri is a pleomorphic, intracytoplasmic parasite of endothelial cells. It produces a proliferative endangiitis of small blood vessels which may result in their occlusion, and endothelial damage to large blood vessels may initiate thrombus formation. Nodular mononuclear deposits occur in perivascular regions of small vessels. Blood vessels of the brain and skin are the most severely affected.

The disease has an incubation period of about twelve days. Most cases begin with a chill, some with severe headache, nausea and vomiting, fever or pain in the chest, back, abdomen or limbs. Most patients develop an eruption on about the fifth day in the axillae, on the trunk or on the inner surface of the arms, consisting of non-pruritic, macular lesions which blanch on diascopy. The rash spreads to the trunk and limbs but the palms and face are not usually affected. Other features of the disease are listed in Table 3. There may be intermittent chills and morning remissions, and the fever ends by rapid lysis or occasionally by crisis after about twelve days. The most common complication is bronchopneumonia. Most deaths occur between the ninth and twelfth days.

TABLE 3
Frequency of Symptoms, Signs, and Complications in Murine Typhus.

	per cent of cases[29]
headache	85
stupor	30
photophobia	17
conjunctival injection	50
myalgia	90
eruption	82
cough	60
cyanosis	4
bronchopneumonia	5
nausea, vomiting or both	35
constipation	25
diarrhea	10
abdominal pain	20
palpable spleen	30
albuminuria	17

Tetracycline is the drug of choice; chloramphenicol is also effective but is itself dangerous. Sulfonamides are contraindicated in Rickettsial disease. Relapses may occur if treatment is stopped prematurely. The disease produces natural immunity against reinfection. It is nationally notifiable.[31]

PREVENTION AND CONTROL

The most important means to prevent endemic typhus and plague is to control their reservoirs and vectors. If an epidemic has begun, fleas must be controlled

before rodents are destroyed lest the fleas leave their dead hosts in search of other victims.

Rat fleas have been controlled by placing cotton plugs containing DDT or benzene hexachloride in rat burrows.[25] Rat runs or buildings known to contain rats may be dusted with DDT. It is extremely difficult to control the fleas of plague-infected wild rodents. Attempts have been made to control sylvatic plague with DDT; however, DDT-resistant *Pulex*,[3] *Ctenocephalides*[3] *and Xenopsylla cheopis*[33] have been encountered.

Once rodent fleas have been controlled, the rodents may be trapped or killed with pesticides such as Warfarin. Garbage dumps and buildings which contain food should be rat-proofed. Dieldrin and toxaphene have been used with limited success against wild rodents.

Flea infestations of individuals may be treated with insecticides and repellants as well as non-specific measures. Repellants can provide up to 90 per cent protection against fleas.[34] The use of flea repellants is not adequate for inhabitants of infested buildings, but may be used for those who experience brief exposures to such fleas as *Tunga penetrans*. N,N-diethyl-n-toluamide (deet) in Johnson's Off, 2-ethyl-1,3-hexanediol in Union Carbide's 6.12, and Indalone will repel fleas.[10] These agents may produce a burning sensation in the eyes, mucous membranes or cuts, and may damage plastics and synthetic fibres. They may be applied to skin, socks, trouser ends, collars and cuffs. Clothes can be soaked in 5 per cent benzyl benzoate or other repellants, but benzyl benzoate is not usually applied to the skin for flea infestations.

The first step is to identify the flea responsible for the infestation. This is especially important in farm families in whom the type of infestation will determine the control measures to be used.[35] If the infestation originates inside the house, five pounds of flaked naphthalene may be spread on the floors of each room and left in place one day. Salt water may be applied to the floors of basements, sheds and barns to kill larvae. The floors may then be vacuumed. Organic debris beneath carpets and in floor cracks should be kept to a minimum. Fleas are susceptible to dryness: damp mopping may encourage their development and vacuuming prevents their proliferation.

It is best to remove the dogs and cats of infested families; however, if the pets are to remain they should be dusted with naphthalene, pyrethrins, rotenone or malathion.[3, 4] Malathion should not be used on young puppies or cats. Gamma benzene hexachloride should not be used on cats. Animals' bedding will require dusting with insecticides. Animals should not become wet while wearing flea collars, and it may be dangerous for an animal to perspire heavily while wearing one.[36]

Chicken and pig farms are frequently infested with fleas which attack humans. Kerosene, gasoline or engine oil may be spread in pigpens and the pigs may be washed with gasoline. Chicken stick-tight fleas are a tremendous nuisance and must have derris powder or carbolated vasoline directly applied to them.

Ten commercial Toronto exterminators were surveyed and it was found that the price charged for flea extermination is usually $9.00 per room. Generally, a three month guarantee is offered. These operators use malathion and other anticholinesterase agents which are very effective against fleas living in stuffed furniture and carpets.

Fleas are annoyingly difficult and expensive to destroy. They represent a serious threat as vectors of disease and more effective means are needed to control them. There is hope that certain microsporidia (protozoa) or other natural enemies of fleas may be employed to do the job.[3, 5] Until then:

The arithmetic flea
Adds to your misery
Subtracts your pleasure
Divides your attention
And multiplies like the devil.[1]

ACKNOWLEDGEMENTS

The author wishes to thank Drs. J. Morgan, Department of Microbiology, New Mount Sinai Hospital, and S. B. McIver, Department of Microbiology and Parasitology, University of Toronto, for their helpful advice.

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Susan Ross, 7T9

Book Review

THE RELATION BETWEEN PHYSICAL AND MENTAL ILLNESS

Michael Robin Eastwood*

University of Toronto Press, No. 4 in the Clarke Institute of Psyehiatry Monograph Series

(119 pages) $10.00

If you don't believe there's any relation between physical and mental illness, this little book probably won't convinee you there is. If you *do* believe, however, or will coneede the possibility, you will probably find Dr. Eastwood's exposition reinforcing. He does not attempt to prove any eause-effeet relationship (the pathogenesis debate has been notoriously unproduetive), but rather to establish a signifieant and positive *association* between the two, in a way that minimizes the bias apparent in previous studies. In this he sueeeeds.

Dr. Eastwood begins with a whirlwind tour through three thousand years of ehanging coneepts of mind and body. He makes brief stops at the supernaturalism of primitive man, the naturalistic beliefs of the Greeks (Hippoerates, Galen, Aristotle), Dark Ages demonology, and finally takes a look at the Cartesian dualism *versus* monism debate of the Renaissanee, whieh has continued to the present day. The emergenee of the psyehoanalytic movement of the twentieth century has been aeeompanied by a revival of the holistie view in medieine and the birth of "psyehosomatie medieine". To quote:

> *The World Health Organization (WHO) report on psychosomatic disorders (1964) states: "The individual is conceived as a complex dynamic system in an unstable state of equilibrium, acting and reacting to changes in the environment and to changes within the system. In disorder, that is disturbance of homeostasis, many aspects of the system are affected. When we speak of psychological processes and physiological processes, we are speaking of different ways of approaching one phenomenon. The phenomenon is not so divided. In this sense, then, there is neither psychogenic nor somatogenic disease, but only disease."* (Emphasis added) (p 7)

This basic tenet seems to have been the *raison d'etre* of empirical studies of the past forty years in this field. Seores of eommunity surveys and elinieal studies, approaehing the problem from both aspects (ie, eoneentrating on the physieal health of persons diagnosed as having psyehiatrie illness, or studying the mental health of physieally ill persons), have offered mixed evidenee for the existenee of a relation between physical and mental disorder. Eastwood highlights the inconsistent findings of a number of sueh studies before eonsidering the varied problems of method and design, subjeet seleetion, and consistent and reliable measurement and evaluation of physical, and more importantly, psyehiatric morbidity. Such methodological issues have been and remain the outstanding difficulties in psychiatric epidemiology.

Eastwood confronts such problems head-on in his own nine month study of a homogeneous population of over two thousand 40 to 64 year-olds in a borough of London, England. After the application of a four part screening procedure – eonsisting of (1) a self-administered questionnaire; (2) a psyehiatric interview (*all* done by Dr. Eastwood); (3) a physieal sereening examination by aneillary personnel; and (4) an aetual physical examination by a general praetitioner – index and control groups were matched by age, sex, marital status and social class. The result was 37 matched pairs of men and 87 matched pairs of women. The index group consisted of those seoring on five or more psychiatric items on the questionnaire and also diagnosed as suffering from a psychiatrie disorder. The members of the control groups were all zero seorers.

His data point to several overall conclusions. The average number of major physical conditions (ie, life-threatening or potentially so) was significantly greater in index groups than among controls. On the average, index cases also had more *multiple* conditions and fewer of them were *free* from physieal disease. The distribution of minor physieal illness did not follow the same pattern. Older groups of both sexes suffered more major physieal disorders than younger groups, and females had major physical disorders involving more body symptoms than men. Patients with a greater severity of psyehiatric illness showed a greater number of major physical disorders as well. The average number of major "psychosomatic" conditions was significantly greater in the index groups than in the controls. Diseases of the cardiovaseular and respiratory systems predominated in both the major and minor physical disorders found in the index group. (In an interesting aside, Eastwood notes that smoking habits were practieally *identical* between the index and eontrol groups.)

He concludes with some possible interpretations of his findings, as well as some suggestions for future epidemiologieal researehers. For example, the relation between stress and coronary heart disease should be tested using classie epidemiological methodology. An accurate epidemiological method should also be devised for distinguishing between chronic bronehitis, emphysema, asthma and the secondary effects of heart disease, to properly examine the relationship between psychiatrie disorder and chronic respiratory disease. And overall:

> *The concept of man having a generalized psychophysical propensity to disease appears to be a useful and alternative model to the one which seeks only specific cause-and-effect relationships. The notion of multiple aetiology in disease, and multiple responses by man to agents threatening his health, is a greater acceptance of the realities of the ecology of ill health.* (p 87)

*Associate Professor of Psychiatry, University of Toronto. Staff Psychiatrist with the Clinical Investigation Unit at the Clarke Institute of Psychiatry, Toronto.

Nor is the clinician overlooked. Due to the changing pattern of disease over time, noncommunicable disorders, particularly psychiatric disorders, are assuming in an ever increasing degree the dubious distinction of being *the* major health problem of well-developed countries. As such, perhaps the general practitioner's attitude, skill and experience with all forms of psychiatric morbidity should be more fully developed. This suggestion is in light of Eastwood's rather distressing finding that 40 per cent of the men and 52 per cent of the women had psychiatric conditions unrecognized by their physicians at the time of the screening surveys. He leaves us with the injunction:

> *The future role of medical practice lies in prophylaxis, whether it be primary prevention, that is, preventing healthy people from developing disease, or secondary prevention, mitigating or eliminating the effects of already established disease.* (Emphasis added) (p 88)

In a land "blessed" with a government health insurance program, this aim would appear to be eminently reasonable. Its desirability is above question. Knowing more about the association between psychiatric disorder and all types of physical morbidity is a big step in the right direction.

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Clinicopathological Conference: Post-Mastectomy Hypercalcemia

T. D. Ruddy, 7T7
R. C. Lo, 7T7

CASE PRESENTATION

A 59 year old woman was admitted to hospital with the complaint of back pain.

Fourteen months prior to admission she had a left radical mastectomy for infiltrative scirrhous adenocarcinoma. Nine months later she became febrile, easily fatigued, and noted the gradual onset of low back pain. She had lost ten pounds since the mastectomy.

Physical examination at that time showed a moderatcly obese female in some discomfort on movement in bed. The vital signs were stable with a temperature of 38°C, pulse 22 per minute and respiratory rate of 20 per minute. The blood pressure was 155/100 mm Hg. A healcd mastectomy scar was visiblc. Examination of the abdomen was unremarkable. There was tenderness to palpation over the region of L4. The knee jerk was diminished and the ankle jerk was absent on the left side.

Urinalysis showed 1+ protein. The hemoglobin was 12 gm per cent and the white cell count was 9500. Serum calcium was 15.8 mg, serum phosphorus 2.6 mg and total protein was 6.8 gm (with albumin 4.6 gm and globulin 2.2 gm) per 100 ml. X-ray films of the spine showed extensive destruction of the transverse process and body of the fourth lumbar vertebra (L4) with compression on the left side. The third, fourth and fifth lumbar vertebrae were osteoporotic.

Radiation therapy was given to the spine and cortisone therapy was begun. The patient's pain disappeared and she was discharged from hospital much improved.

She continued on cortisone and remained well until one week before this admission when she developed crampy epigastric and back pain which lasted about an hour. She was also suffering from nausea and fatigue.

Examination on admission revealed a woman demonstrating features of Cushing's syndrome with an increasc in the size of the face and torso. Her hemoglobin this time was 10.3 gm per cent, and serum calcium was 2.8 mg per cent with phosphorous 13 mg per cent.

On the seventh hospital day an attack of syncope occurred during a bowel movement. About an hour later she developed severe rctrosternal distress of fifteen minutes duration with an abnormal electrocardiogram. She bccame suddenly dyspneic a fews days later and died.

CLINICAL DISCUSSION

Hypercalcemia may be a complication of almost any malignancy but is most commonly associated with carcinoma of the breast, lung or prostrate and with myeloma.

Several mechanisms have been proposed to explain the development of hypercalcemia associated with malignancy. Increased skeletal resorption due to osteolytic metastascs could result in calcium release into the extracellular fluid in excess of the capacity of homeostatic mechanisms. The formation of bony metastases may be related to prostaglandin activity. Greater amounts of prostaglandin-like material have been found in malignant breast tumours than in normal breast tissue from the same patient or in benign tumours. In addition, tumours with high levels of prostaglandin-like material have been associated with bony metastases. Since some prostaglandins arc potent bone-resorbing substances they may aid in the formation of these bony metastases. Prostaglandin determinations might bc useful in predicting the spread of tumour, and inhibitors of prostaglandin synthesis might delay that spread.[1] Ectopic production of parathyroid hormone by the neoplasm could explain cases in which skeletal metastascs have not been found. Instances have been documented where the radioimmunoassay for parathormone measures elevated levels of a parathormone-like polypeptide in the plasma of affected patients and in tumour tissue.[2] However, the structure and immunological activity of this polypeptide differs from that secreted by normal, adenomatous or hyperplastic glands.[3] Perhaps neoplasia may induce the formation of a precursor of parathormone. Other hormonal mechanisms havc been suggested to implicate vitamin D-like sterols and prostaglandins.

The protean clinical manifestations of hypercalcemia are influenced in part by the level of serum calcium and by associated conditions such as alkalosis, dehydration or hypokalemia. The earliest symptom is often weakness and fatigue. The patient may also complain of anorexia, constipation, nausea and vomiting when the serum calcium exceeds 12 mg per cent. Polyuria and secondary polydipsia may result from hypercalcemic nephropathy compromising renal concentration. Pancreatitis, hypertension and arrhythmias may occur. Dehydration and azotemia with metabolic alkalosis may develop when the extracellular fluid volume can no longer be maintained. Sudden death is always a serious risk when the serum calcium exceeds 15 mg per cent. Grave errors in management can occur if a hypercalcemic crisis is mistakenly diagnosed as cachexia, ccrebral metastasis or drug toxicity.

The differential diagnosis of hypercalcemia in our case should include bone metastascs, primary hyperparathyroidism and immobilization hypercalcemic osteoporosis. Anemia and metabolic alkalosis and elevation of the serum alkaline phosphatase level are evidence of malignant disease. Hypophosphatemia may be seen in malignancy with or without ectopic parathyroid hormonc production and should not be considered supportive of primary hyperparathyroidism.[4] In the absence of vomiting or diuretic administration, a serum chloridc less than 102 mEq per litre is evidence precluding the diagnosis of primary hyperparathyroidism.[5] Remember that hypercalcemia may be unrelated to any

demonstrable malignancy. If primary hyperparathyroidism cannot be eliminated by clinical and laboratory investigations, and the patient has a malignancy with a favourable outlook, selective cathcterization of superior cervical veins for parathormone assay may aid in diagnosis by demonstrating a "step-up" in parathormone concentration from a parathyroid hyperplasia or adenoma.

Bone metastases at L3, L4 and L5 are the most likely cause of hypercalcemia in this case. The most common architectural alteration produced by this lesion is osteolytic destruction with a characteristic moth-eaten appearance on x-ray. Bones most frequently involved are the lumbar vertebrae and the pelvis. Pathological fractures occur in 15 per cent of cases. The patient characteristically has back pain which tends to radiate downward and is aggravated by motion. When there is compression of the spinal cord, tendon reflexes corresponding to that spinal segment are diminished.

The decision to treat hypercalcemia in a patient with neoplasia should not be made without consideration for the individual patient. Hypercalcemic crisis may be a merciful termination of intractable incessant pain. However, symptoms of hypercalcemia may be confused with those due to malignancy and decisive treatment of the hypercalcemia may be the only way to clarify the issue. Effective therapy will not only provide symptomatic relief but will also optimize ongoing tumour treatment.

Radiation therapy has been successful in normalizing the serum calcium in patients with extensive bony metastases as in this case. Adequate salt and water intake is essential to prevent dehydration which would aggravate the hypercalcemia by compromising renal function. Vitamin D, thiazides, absorbable antacids and other agents increasing serum calcium levels should be avoided. Cardiac glycosides must be used with caution since they potentiate hypercalcemia by inotropic and toxic effects. Immobilization which increases the rate of skeletal resorption should be prevented. Since the majority of serum calcium is derived from bone, dietary restriction is of little valuc. Glucocorticoids have an anti-vitamin D effect and may decrease the rate of skeletal resorption and calcium absorption from the the gut. Oral phosphates in dosages of 2 to 5 grams daily may be useful in mild hypercalcemia, particularly if the tumour is not responsive to glucocorticoids or cytotoxic therapy.

Higher levels of serum calcium (>15 mg per cent) necessitate intensive treatment. Saline will correct dehydration and increase urinary calcium excretion by increasing sodium delivery to the proximal tubule. Furosemide will further promote diuresis of sodium and calcium. Mithramycin, an antibiotic with cytotoxic activity, may be useful through its ability to block the the effects of parathormone and possibly of vitamin D on bone.[6] The benefits derived from dialysis are too transient to be of value. Calcitonin is partially effective in lowering serum calcium and requires frequent injection. The intravenous administration of phosphates carries with it the possibility of metastatic calcification and acute renal failure.

The hypercalcemia in this case presentation was effectively treated with radiation to the spine and long-term corticosteroid therapy. The features presented by the patient on admission may be attributed to the exogenous administration of steroids. Metabolic effects result in fat redistribution. Peptic ulceration with bleeding account for the crampy epigastric pain and the low hemoglobin. Hypocalcemia and hyperphosphatemia were the result of the anti-vitamin D effect of steroids, and also the possible remission of bone metastases.

The cause of death was probably acute cor pulmonale from pulmonary thromboembolism.

PATHOLOGICAL DISCUSSION

At autopsy metastatic carcinoma was found in the lungs bilaterally, liver, peritoneal cavity, lymph nodes of the left internal mammary chain, mediastinal and paraaortic nodes and the entire vertebral column, having produced marked destruction of L3, L4 and L5.

Metastatic spread of breast carcinoma may be hematogenous, lymphatic or both. At the time of diagnosis approximately 70 per cent of patients with breast carcinoma will have regional lymph node metastases indicating the ability of cancer cells to grow independently of the primary tumour. As a result, distant metastases to bone and other organs may be expected. In most instances remote metastases are the result of hematogenous dissemination. The major route is via the thoracic duct to the innominate vein into the right side of the heart. From here tumour cells are scattered throughout the lung vasculature where they are trapped by small arteriolar branches. Some survive and infiltrate lung parenchyma; others are engulfed by the protective fibrous tissue stroma. Thus, lung metastases are usually well established before seeding of liver, bone, ovary, adrenal and spleen takes place. Secondary foci occasionally occur in bone, brain and ovary because of invasion of the vertebral vein and azygous system. This manner of spread is common in the development of metastases that appear in the lower vertebrae and pelvis. Tumour cells may disseminate widely without ever entering the heart and general circulation.

On gross examination the tumour masses were noted to be hard and greyish-white in colour. Microscopic examination showed many islands of poorly differentiated small anaplastic cells scattered throughout collagenous desmoplastic stroma.

As the disease advances with wider metastatic spread the carcinoma tends to become more anaplastic and less differentiated.

Unexpectedly, a small parathyroid adenoma was found. Grossly the adenoma appeared small, yellow-brown, soft, and weighed about one gram. Histologically the lesion contained solid sheets of chief cells (wasserhelle cells) and oxyphil cells.

Parathyroid hormone secreted by the adenoma may have contributed to the hypercalcemia assumed to be

due to bony metastases from breast carcinoma. Had the adenoma been surgically excised a lower dosage of corticosteroids would have been effective in controlling the hypercalcemia and perhaps could have avoided the development of Cushing's syndrome.

The patient's death was found to be the result of multiple thromboemboli scattered in the periphery of the lung fields.

ACKNOWLEDGEMENT

We are indebted to Dr. E. B. Tovee, Department of Surgery, Toronto General Hospital, for his generous assistance.

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*M. A. Baker, M.D.**

Book Review

THE ROLE OF IMMUNOLOGICAL FACTORS IN VIRAL AND ONCOGENIC PROCESSES

The John Hopkins University Press, Baltimore, 1974. 480 pages. $22.50

Fads and fancies come and go in biomedical research with the same frequency as clothing styles, but some avenues of investigation achieve sufficient import and popularity to merit the cliché "literature explosion". Studies of the relationship of the immune system to cancer have achieved this notoriety. The volume under review is a compendium of papers and discussions by researchers invited to an international symposium by Miles Laboratories Inc. The conference was held in Baltimore and then moved to Vienna and thus attracted a wide range of prominent investigators in both the basic and clinical aspects of tumour immunology. The 480 pages of text provide a highly detailed review of much of the field under investigation in the two or three years preceding the conference. Professor George Klein reviews Herpes viruses and oncogenesis, the Drs. Hellstrom review their studies of lymphocyte mediated cytotoxicity to tumour antigens, and Donald Morton's group reviews clinical and experimental trials of BCG immunotherapy. Other topics stressed include the immunology of animal tumour viruses, malignancies in immunodepression, embryonic tumour antigens such as CEA, and cell surface characteristics of malignant cells. Over 125 speakers and discussants are recorded and very little has been left unsaid.

Perhaps the single most important subject considered is the one, reserved for the last chapter, that considers antigenic properties of surfaces of malignant and normal cells. As R. A. Knight *et al* point out, the attempt to understand the topographical relationship of antigens to one another and to the cell surface as a whole, differs from traditional immunological approaches concerned with the structure of individual antigens. The technique "cocapping" is able to separate antigens topographically and thereby to assess alleged identity of antigens. Analysis of the relations between "inducer" and "helper" determinants and consequent considerations of "immunogenicity" may help in understanding the relationship of antigenic structural make-up to the cellular components of the immune response. The studies of Burger *et al* summarize the important correlations between cell surface alterations and the transformed state in tissue culture cells particularly as the alterations affect lecitin agglutinability. Inbar and Sachs assess the mobility of carbohydrate containing structures on the surface membrane of normal and malignant transformed cells. The articles in this last section are the best indicators of the direction of investigations since the 1973 conference.

The volume as compiled is of major usefulness only to other investigators in the field of tumour immunology. The experimental detail is much too great and the conclusions much too tentative for use in medical student education or the continuing education of practicing physicians. Considering that the "literature explosion" in tumour immunology has continued unabated since the publication of this volume, the usefulness even to investigators must necessarily be limited by the mid-1973 date of a conference which was designed to discuss work completed in previous months or years. The index is excellent for this type of publication and the glossary of acronyms is most helpful. Duplication of subject matter arising from the conference's dual location renders the table of contents and the organization of papers somewhat confusing. I would conclude that investigators interested in tumour immunology could find this volume useful as a reference source for work in the field up to the 1972-73 period.

*Toronto Western Hospital

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